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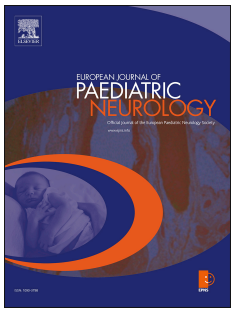

Stable cognitive functioning with improved perceptual reasoning in children with dyskinetic cerebral palsy and other secondary dystonias after deep brain stimulation

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Stable cognitive functioning with improved perceptual reasoning in children with dyskinetic cerebral palsy and other secondary dystonias after deep brain stimulation.

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Original Article

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What this paper adds

Cognitive function after globus pallidus internus (GPi) deep brain stimulation (DBS) was stable in 40 children with secondary dystonia

The picture completion subset of the perceptual reasoning ability improved after GPi DBS

These post GPi DBS results should be interpreted with caution given the heterogeneous aetiology and age ranges of this small secondary dystonia retrospective cohort

ABSTRACT

Background: Dystonia is characterised by involuntary movements (twisting, writhing and jerking) and postures. Secondary dystonias are described as a heterogeneous group of disorders with both exogenous and endogenous causes. There is a growing body of literature on the effects of deep brain stimulation (DBS) surgery on the motor function in childhood secondary dystonias, however research on cognitive function after DBS is scarce.

Methods: Cognitive function was measured in a cohort of 40 children with secondary dystonia following DBS surgery using a retrospective repeated measures design. Baseline pre-DBS neuropsychological measures were compared to scores obtained at least one year following DBS. Cognitive function was assessed using standardised measures of intellectual ability and memory.

Results: There was no significant change in the assessed domains of cognitive function following DBS surgery. A significant improvement across the group was found on the Picture Completion subtest, measuring perceptual reasoning ability, following DBS.

Conclusion: Cognition remained stable in children with secondary dystonia following DBS surgery, with some improvements noted in a domain of perceptual reasoning. Further research with a larger sample is necessary to further explore this, in particular to further subdivide this group to account for its heterogeneity. This preliminary data has potentially positive implications for the impact of DBS on cognitive functioning within the childhood secondary dystonia population.

INTRODUCTION

Dystonia is a movement disorder characterised by involuntary, sustained muscle contractions resulting in twisting, repetitive movements and abnormal postures[1, 2] and has been aetiologically classified as falling within either a primary or secondary group[3]. Secondary dystonias are described as a heterogeneous group of disorders with both exogenous and endogenous causes, including dyskinetic cerebral palsy[4,5] (CP), hypoxic-ischaemic, inflammatory and neuro-metabolic conditions such as hyperbilirubinaemia, glutaric aciduria type-I and mitochondrial disorders[4,5]. The secondary dystonia group also encompasses neuro-degenerative conditions, such as neuro-degeneration with brain iron accumulation (NBIA) [6]. Considering the heterogeneity that exists within the dystonia population it is important to separately explore the varying diagnoses due to the differing phenotypes and varied responses to treatment[7].

Deep brain stimulation (DBS) of the internal globus pallidus (GPi) has been used to successfully manage dystonia, in both children and adults with a diagnosis of primary dystonia [8, 9,10]. With more modest improvements than the primary dystonia group, recent studies have highlighted the benefits of DBS for motor function in children and adults with secondary dystonias [11, 12, 13]. The management of movement disorders in children is complex and lacks class I evidence of efficacy[14]. The main criteria for considering DBS within this group is the reported poor quality of life and high disability that is not responsive to medical treatment[15].

While our understanding of the motor impact of DBS on dystonia broadens, there is still much to be learnt about the non-motor effects of DBS within the dystonia population. Investigating these effects, in particular cognitive function, has been recommended as part of the overall surgical process[16]. Much of the research to date

has focussed on the cognitive outcomes of DBS surgery within adult primary dystonia populations. Findings within this cohort have been mixed with some studies reporting preserved or improved cognitive function[17] and others reporting a decline across certain domains of function[18]. With regard to the impact of DBS on paediatric cognitive functioning within a primary dystonia group, our group has previously reported individual fluctuations in cognitive function, but overall, cognition largely remains stable before and after DBS surgery[19].

Due to the heterogeneity of the dystonia population, the literature calls for further exploration regarding the possible impact of DBS on cognitive function in individuals with secondary dystonia[19], particularly dyskinetic CP. Research investigating this is currently sparse, particularly within the paediatric group.

Within the adult population, a group of 13 individuals with dyskinetic CP were assessed before and after DBS and it was found that there was no worsening of cognition following surgery[20]. Similar results have been reported within a paediatric population, specifically within a cohort of children with Neurodegeneration with Brain Iron Accumulation (NBIA)[21]. NBIA is a neurodegenerative disorder that has been associated with cognitive decline; hence it is a particular area of interest when investigating the impact of DBS on cognition in secondary dystonia. This study reported no cognitive decline within this group following DBS surgery and indeed, improvements in functioning in certain domains. The researchers suggest that the findings were likely to be a result of improved concentration and access to test materials after DBS dystonia moderation.

There is a need for further research to explore these preliminary findings and broaden our understanding of cognition after DBS within the paediatric secondary dystonia population. This is an important area of study due to the developing nature of the child's brain, and is needed in order to broaden the evidence-base for this population. Our objective was to assess global cognitive ability and memory in a group of children with secondary dystonia who have undergone bilateral pallidal DBS.

METHOD

Design:

This is a retrospective study of a cohort of 40 children and young people with secondary dystonia using a within groups design. All patients were under the care of a tertiary hospital specialist complex motor disorders service (CMDS). All assessments were performed routinely as part of the service's clinical protocol between 2007 and 2015 and the data constitutes a service evaluation for which ethical approval is not required.

Participants:

All patients under the care of the service with a confirmed diagnosis of secondary static or secondary progressive dystonia and at least one year follow up data post-DBS were included in this study (n=40). Thirty three patients had a secondary static and seven patients had a secondary progresssive dystonia. Patients were diagnosed and classified by the Consultant Paediatric Neurologist (JPL). The mean age of participants at the time of surgery was 12.5 years (SD = 3.53; range = 5 to 18 years). Nineteen patients were male and 21 were female. Twenty-two/40 had a diagnosis of

CP which is the commonest cause of dystonia in childhood. All patients with NBIA experienced blepharospasms.

DBS surgery was performed under general anaesthetic using MRI-guided postero-latero-ventral globus pallidus targeting as reported elsewhere[22].

Measures:

Cognitive functioning was assessed using standardised measures. For each child, the measures used depended on their age and ability to physically and verbally access the materials. The measures used were:

1. **Non-verbal intellectual abilities:** The Perceptual Reasoning Index subtests of the Wechsler Scales of Intelligence IV: (WISC-IV)[23] and Wechsler Abbreviated Scales of Intelligence (WASI) [24] (Block Design, Matrix Reasoning, Picture Concepts, and Picture Completion) were used to measure non-verbal intelligence, including visuo-spatial, abstract, and conceptual reasoning skills.
2. **Verbal intellectual abilities:** The Verbal Comprehension Index subtests of the WISC-IV[23] and WASI[24] (Vocabulary, Similarities, Comprehension) were used to measure understanding of verbal concepts, social rules, and vocabulary.
3. **Memory:** Immediate and delayed verbal and visual recall were assessed using Faces and Stories [subtests of the Children's Memory Scale (CMS) [25] and the Faces and Logical Memory Wechsler Memory Scales (WMS)] [26]. Working memory, the ability to mentally retain and manipulate verbal information, was measured using the Working Memory Index subtests (Digit Span and Letter-Number Sequencing) of the WISC-IV[23].

Procedure:

All patients were assessed by a clinical psychologist as part of a routine baseline assessment prior to DBS surgery and then at post-DBS clinical follow-up between one to three years post-surgery. The variation in follow-up times was due to the fact that there was approximately a two year period where the service lacked full access to clinical psychology support and some assessments were subsequently delayed. Picture Completion was substituted for Block Design on administration of the WISC-IV due to difficulties with hand function that existed within the cohort and the picture completion subtest requires less hand function ability. Subtests with a verbal component (e.g. Verbal Comprehension and Working memory subtests of the WISC IV and the verbal memory subtests of the CMS and WMS) were not administered to children who were non-verbal (n=19). Due to the impact of movements on fatigue and the time taken to complete the subtests, it was not possible to complete the full battery of assessments with all the patients. As compared to cognitive testing carried out with a non-dystonic population, these assessments were conducted over a longer period of time to accommodate for movements, including blepharospasms and children were given regular breaks.

The WMS and WASI are both normed on adult populations and were administered to the young people over the ages of 16 (n=12).

Data analysis:

Due to the variability of the within subject subtest scaled scored, analysis was performed on the scaled scores, rather than the Index scores. This is because it is not valid to report Index scores when there is a significant subtest scatter. For the

purposes of analysis, corresponding subtests from the WISC and WAIS and CMS and WMS were grouped together. Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). As the data was not normally distributed, non-parametric tests of significance were used. Post-operative cognitive scores were compared with baseline scores using the Wilcoxon signed-rank test.

RESULTS

Demographic Information

Demographic and assessment details are presented in Table 1. Previous investigations have confirmed a reduction in dystonia within this particular cohort of children[10, 27]. Details of individual changes in medication following surgery are presented as a supplementary table.

Table 1: Demographic information for secondary dystonia cohort

Diagnosis	No. of males	No. of females	Mean age at time of surgery (years)	WISC IV subtests administered		CMS subtests administered	
				Verbal patients	NonVerbal patients	Verbal patients	NonVerbal patients
Cerebral Palsy	9	13	13	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	Picture Con Matrix Reas Picture Comp	Stories Faces	Faces
NBIA	1	4	12.8	Similarities Vocabulary Matrix Reas	Matrix Reas Picture Comp	-**	-**
Lesch-Nyhan	2	0	12	Picture Con * Matrix Reas Picture Comp	NA	-**	-**
Congenital Neuromuscular Disorder	0	1	9	Similarities Vocabulary Comprehension Picture Con	NA	-**	-**

				Matrix Reas Picture Comp			
Polymicrogyria	0	1	13	NA	Matrix Reas	-**	-**
Mitochondrial Disorder	1	1	6	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	Picture Con Matrix Reas	Stories Faces	-**
Glutaric Aciduria Type 1	3	0	14	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	Picture Con Matrix Reas Picture Comp	Stories Faces	Faces
Cerebrovascular Accident	1	0	13	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	NA	Stories Faces	NA
Traumatic Brain Injury	1	0	17	NA	Vocabulary*** Picture Con Matrix Reas	NA	-**
Hypoxic Ischaemic Encephalopathy	0	1	11	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	NA	-**	-**
Neonatal Meningitis	0	1	16	Similarities Vocabulary Comprehension Picture Con Matrix Reas Picture Comp	NA	-**	NA

*Due to the fact that speech had an impact on postures and, therefore, increased the burden of testing in these patients, only non-verbal subtests were administered.

** CMS subtests were not administered to some patients due to time constraints within the clinical setting. Such constraints included burden of testing and the length of time it took to complete the battery of assessments with certain patients due to the impact of their dystonia.

***It was possible to administer the Vocabulary subtest to this nonverbal patient as they had enough hand function to answer the questions on an iPad.

Results of Cognitive Testing

Global Cognitive Function (WISC IV)

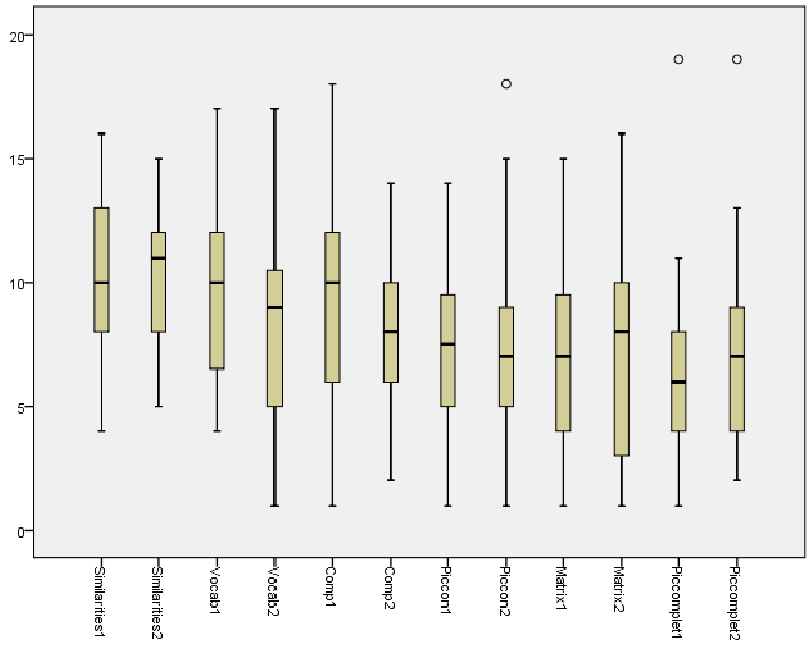
Verbal Comprehension Ability

Verbal Comprehension subtests were administered to 21/40 patients. There were no significant differences found between the group's Similarities scores before (Mdn = 10) and after (Mdn = 11) surgery, Z = -0.46, p = 21, r = 0.65. There were no significant differences found between the group's Vocabulary scores before (Mdn = 10) and after (Mdn = 9) surgery, Z = -1.65, p =21, r = 0.1. Finally, there were no significant differences found between the group's Comprehension scores before (Mdn = 10) and after (Mdn = 8) surgery, Z = - 1.67, p = 21, r = 0.1).

Perceptual Reasoning Ability

The Picture Concepts subtest was administered to 28/40 children and no significant differences were found between the group's scores before (Mdn = 7.5) and after (Mdn = 7) surgery, Z = -0.33, p = 28, r = 0.75. The Matrix Reasoning subtests was completed by 35/40 children and no significant differences were found between the group's scores before (Mdn = 7) and after (Mdn = 8) surgery, Z = -0.65, p = 35, r = 0.55. Lastly, the Picture Completion subtest was completed by 25/40 children. A significant improvement was found between children's Picture Completion scores before (Mdn = 6) and after (Mdn = 7) surgery, Z = -1.97, p = 25, r = 0.5.

Figure 1: Verbal comprehension and perceptual reasoning scores before and after surgery

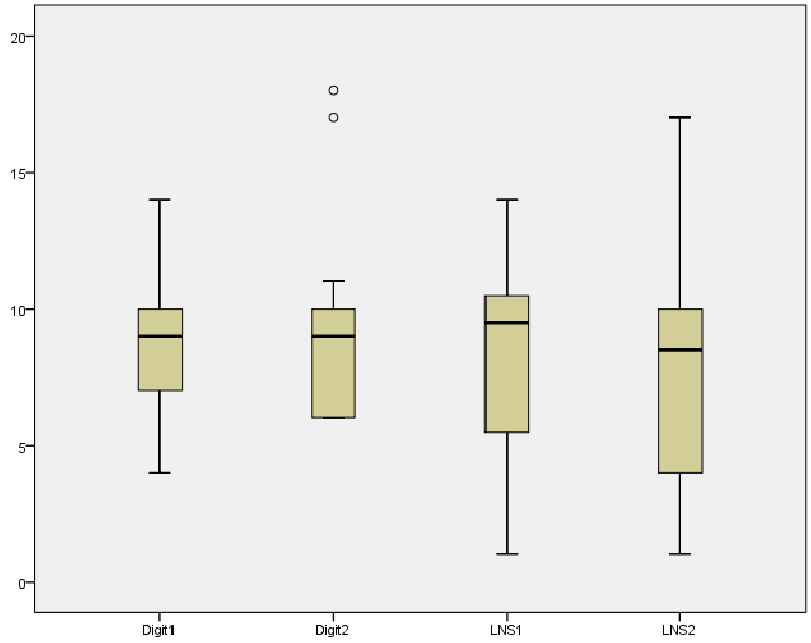


Memory Ability

Working Memory Ability

The Digit Span subtest was administered to 13/40 children and no significant differences were found between the group's scores before (Mdn = 9) and after (Mdn = 9) surgery, Z = -0.72, p = 13, r = 0.47. The Letter-Number Sequencing subtest was administered to 12 children and, equally, no significant differences were found between the group's scores before (Mdn = 9.5) and after (Mdn = 8.5) surgery, Z = -0.26, p = 12, r = 0.8.

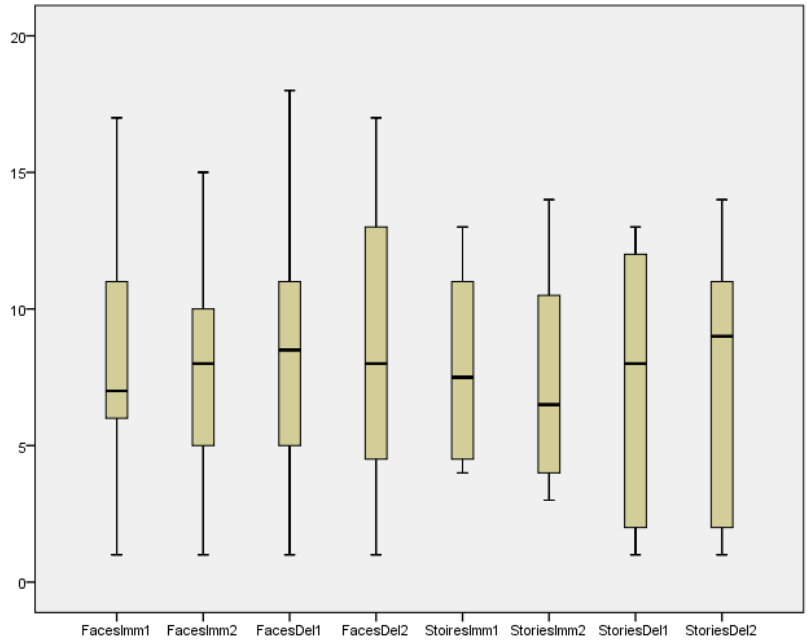
Figure 2: Working memory scores before and after surgery



Immediate and Delayed Visual Memory

The Faces subtests of the CMS and WMS were administered to 13/40 children. No significant differences were found between the group's immediate recall scores before (Mdn = 7) and after (Mdn = 8) surgery, Z = -0.52, p = 13, r = 0.96 or their delayed recall before (Mdn = 8.5) and after (Mdn = 8) surgery, Z = -0.18, p = 13, r = 0.86. The Stories and Logical Memory subtests of the CMS and WMS were administered to 12 children. No significant differences were found between the group's immediate recall scores before (Mdn = 7.5) and after (Mdn = 6.5) surgery, Z = -0.85, p = 12, r = 0.4 or their delayed recall before (Mdn = 8) and after (Mdn = 9) surgery, Z = -0.17, p = 12, r = 0.87. See Box 1 for a brief illustrative example of the impact of dystonia management on memory function.

Figure 3: Verbal and visual memory scores before and after surgery



Box 1: Illustrative case example

When considering the possibilities of altered cognitive function, it is also important to consider the role of medication. One of the CP cases included in this study subjectively reported worsening verbal memory following DBS and standardised assessment confirmed this (scaled score on the Stories subtest of the CMS reduced from 7 to 2 at two year follow up). The family queried whether DBS was responsible for this decline in function and there was a trial switching-off of the DBS device to test this hypothesis. This did not result in any improvement in memory function and, as a result, the device was switched back on and alternative causes for the memory deterioration were explored. A reduction in medication was subsequently trialled. Prior to DBS the patient was on a dose of Trihexyphenydl 3mgs TBD and, over the course of two years following surgery, this increased to 5 mgs TBD. This medication was given a trial cessation, resulting in a subjective improvement in verbal memory to the extent that the patient no longer reported any difficulties in this area. This case highlights how it is important to gain a baseline measure of cognitive function prior to DBS surgery in order to explore any deterioration.

DISCUSSION

This pilot study examined the cognitive profiles of children and young people with secondary dystonia who had undergone DBS surgery and is the first study to systematically assess cognition following DBS more broadly within a childhood secondary-dystonia population.

Despite the relative small number of children and young people reported in this study, there are a number of important findings.

Overall, there was no significant decline found in cognitive profiles within this group.

The cohort as a whole demonstrated significant improvement in one subtest measuring perceptual reasoning (Picture Concepts). This may have important implications for the impact of DBS on non-motor functioning and tentatively suggests that it did not diminish cognitive function in this sample of children and young people but also appeared to improve certain domains of cognitive function.

The lack of a significant decline within this cohort supports findings from previous research both within paediatric primary[19], adult CP[20] and paediatric NBIA groups[21], who also reported no overall worsening of cognition following DBS surgery. To the authors' knowledge, no previous research has demonstrated the same improvements in areas of perceptual reasoning (picture completion) found in this study. As such, further research is necessary to explore the nature of these improvements, including generalisability across the secondary dystonia population and the action mechanisms behind any improvement.

Improvement in cognitive ability demonstrated in this group may relate to a number of different variables. Firstly, it could be hypothesised that a reduction in dystonia

may lead to improved attention and concentration and therefore enabled patients to better engage with their education in general. It is also possible that children had better physical access to cognitive testing following improvements in dystonia resulting in better scores. Lastly, reductions in medication following surgery may have led to increased alertness and concentration and therefore improved performance on testing.

Further research should consider how any changes in cognition following DBS relate to any changes in dystonia. For instance we have found in childhood cases of neurodegeneration with brain iron accumulation (NBIA) due to the PANK-2 mutation that relative to primary childhood dystonias, there is relatively reduced glucose metabolism in the anterior cingulate which is important when dealing with conflicting information such as Stroop testing[28]. Reduced glucose metabolism was found in bilateral occipital lobes including the midline, lingual and fusiform gyri of children with NBIA. One possible explanation for these findings may be a visual impairment related to a retinal dysfunction reported in NBIA (PANK2) disease, notably in HARP syndrome consisting of hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration[29] leading to reduced occipital lobe activation. Damage to the lingual gyrus has been reported in impaired visual processing[30]. Activation of the lingual gyrus is linked to encoding complex images[31]. Word recognition also relies on the lingual gyrus activity[32] as does naming of stimuli[33,34,35]; word contrast and length[32] and semantic processing[36]. This extends to pairing abstract nouns with visual imagery or sentence generation and the interpretations of the intentions of characters in comic strips[37]. Fluency of retrieval of facts is also linked to the lingual gyrus in children[38]. The hypometabolism in the lingual gyrus is consistent with difficulties experienced by children with NBIA who in addition to their visual

difficulties experience problems speaking and expressing themselves which may be attributed to dystonic dysarthria rather than semantic processing problems or a true aphasia. Asking a child with dystonia secondary to NBIA to speak, comment on a picture or interpret a series of action pictures or comics may provoke an extremely severe burst of total body dystonia including blepharospasm, orolingual dyskinesia, retrocollis and arm dyskinesia. These findings suggest that reduced lingual gyrus activation in NBIA may contribute to task-dependent increases in dystonia whenever the child is presented with visual or complex visual and language tasks which can in turn improve, when dystonia is relieved. Less extreme difficulties in non-NBIA secondary dystonias may also be observed and could therefore improve with dystonia relief.

As previously discussed, in a recent study of the influence of DBS in cognitive performance in children with NBIA[21], tasks with a visual content were often impossible to perform or baseline scores were low. But at 1 or 2 years after DBS most NBIA patients were able to perform testing with visual material including: picture concepts; vocabulary/picture vocabulary; visual immediate and delayed memory; faces immediate and delayed memory. This was interpreted as indicating that relief of dystonia improved access to test materials, including, for instance, reduced blepharospasm allowing better visualization of test materials. However, the reported improved performance after DBS would tie in with the concept of distributed networks of the basal ganglia including sensorimotor, cognitive–associative and limbic as described by Draganski[39], and elaborated by Redgrave[40]. In which case DBS could have a direct impact on cognitive-associative as well as limbic and pain

functions. At this stage this is purely speculative and further research would be required to test this hypothesis.

The primary limitation to this study is the small sample size and the heterogeneity that exists within this secondary dystonia cohort in terms of the specific individual diagnoses within this group. These limitations clearly create a challenge in terms of reliable generalisations. As an area for future investigation, it would be important to further separate the varying diagnostic groups within children presenting with secondary dystonia.

An additional limitation is the varying time points at which children were assessed following surgery. Whilst this was an unavoidable consequence of service constraints, its potential impact on the findings must be acknowledged. Further longitudinal research investigating the longer term impact of DBS on cognitive function would be valuable in order to clarify whether the passage of time following this surgery has any impact on cognition.

CONCLUSION

The current study examined the impact of DBS surgery on cognition in children and young people with secondary dystonia. Results from this study are largely suggestive of preserved cognition in children with secondary dystonia after DBS surgery, with some significant improvement noted in a domain of perceptual reasoning. This provides initial information to tentatively suggest that GPi DBS within this population has no adverse effect on cognition. These findings are particularly important in light of the possible negative impact of other forms of dystonia management, such as medication, on academic function in children[41].

There is a need for further research to explore these initial findings and improve our understanding of cognition following DBS within the paediatric secondary dystonia population. Of particular interest is whether the stimulation of a basal ganglia structure produces changes in cognition due to a direct stimulation of the cognitive system within this structure. It would be beneficial for future research within paediatric DBS for dystonia to focus on the influence of the electrode position within the target structure, as well as the trajectory of the electrode and basal ganglia structures traversed[22] in relation to cognitive changes.

Lastly, access to a larger, multi-centre samples would enable more in-depth exploration of cognition following DBS within the discreet diagnoses that exist within the secondary dystonia cohort of children. For that there will need to be a consensus on the key assessments that are required and protocols to enable psychologists in multidisciplinary teams to consistently adapt access to test materials in similar ways. This information could be used to support families and schools in decision making around DBS and in planning and monitoring changes in education provision following DBS surgery.

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Highlights

Cognitive function after globus pallidus internus (GPi) deep brain stimulation (DBS) was stable in 40 children with secondary dystonia

The picture completion subset of the perceptual reasoning ability improved after GPi DBS

These post GPi DBS results should be interpreted with caution given the heterogeneous aetiology and age ranges of this small secondary dystonia retrospective cohort